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Abstract

In the adult brain, different cell types communicate with each other through cell–cell contacts and brain activity is regulated at the cell membrane. But long before the brain is fully functional, different excitatory and inhibitory cell types generated at distinct places migrate through the developing brain to their final position. The elements guiding these migrating neurons, either structural axonal scaffolds or chemical guidance factors, are relatively well described. However, the molecules involved in the individual short-timed membrane contacts migrating cells make with other cells during their migration process are less well understood. This update focuses on recent novel insights into the molecular nature of these cell–cell contacts and the cross-talk taking place at the cell membrane.

Keywords

neuronal migration, cell interaction, forebrain development, neurodevelopmental disorder, cell membrane

Different Flavors of Neuronal Migration

Different neuronal cell types are generated before or after birth at distinct neurogenic areas, and all of them migrate and intermingle in different regions of the developing forebrain (Fig. 1) (reviewed recently in Evsyukova and others 2013). The Cajal–Retzius cells are among the earliest neurons born and originate from the cortical hem, the ventral pallium, and the septum around embryonic day (E) 10 to 11 (Bielle and others 2005). They migrate tangentially and spread over the cortical surface, guided by secreted cues from the meninges (Borrell and Marín 2006) (Fig. 1A). Pyramidal excitatory neurons born in the ventricular zone of the cortex migrate radially using radial glial processes as a scaffold. Initially, neurons move their soma to the pial surface in a process called somal translocation (Fig. 1A and B). Later-born neurons or intermediate progenitors first detach from their radial glial mother and lose their polarity on entering the intermediate zone. After a transient multipolar stage, the neurons polarize again: one neurite is selected to become the axon, and the neuron readheres to the radial glial scaffold and migrates radially beyond the earlier-born neurons (Fig. 1A and C).

The bulk of GABAergic cortical interneurons is generated in the medial and caudal ganglionic eminence and the pre-optic area (MGE, CGE, and POA, respectively) in the ventral telencephalon. To reach their final position in the cortical plate, interneurons are guided by secreted and membrane-bound factors in defined routes through the ventral telencephalon and cortex. There, they switch to a radial migration mode using the radial glial scaffold to enter into the cortical plate (Fig.1A and D) (Guo and Anton 2014).

Independent of their migration mode, all neurons in the developing brain encounter and interact with other neurons on their way. In this update, we aim to cover recent work describing the molecular nature of cell–cell interactions in the context of neuronal migration in the embryonic forebrain. We focus in particular on those contacts where interacting molecules on both cells were described. Because of space limitations, we do not cover cellular interactions with the extracellular matrix, or signaling mechanisms downstream of these membrane interactions, and we refer to Scales and Parsons (2011) and Khodosevich and Monyer (2011) for reviews on these matters.

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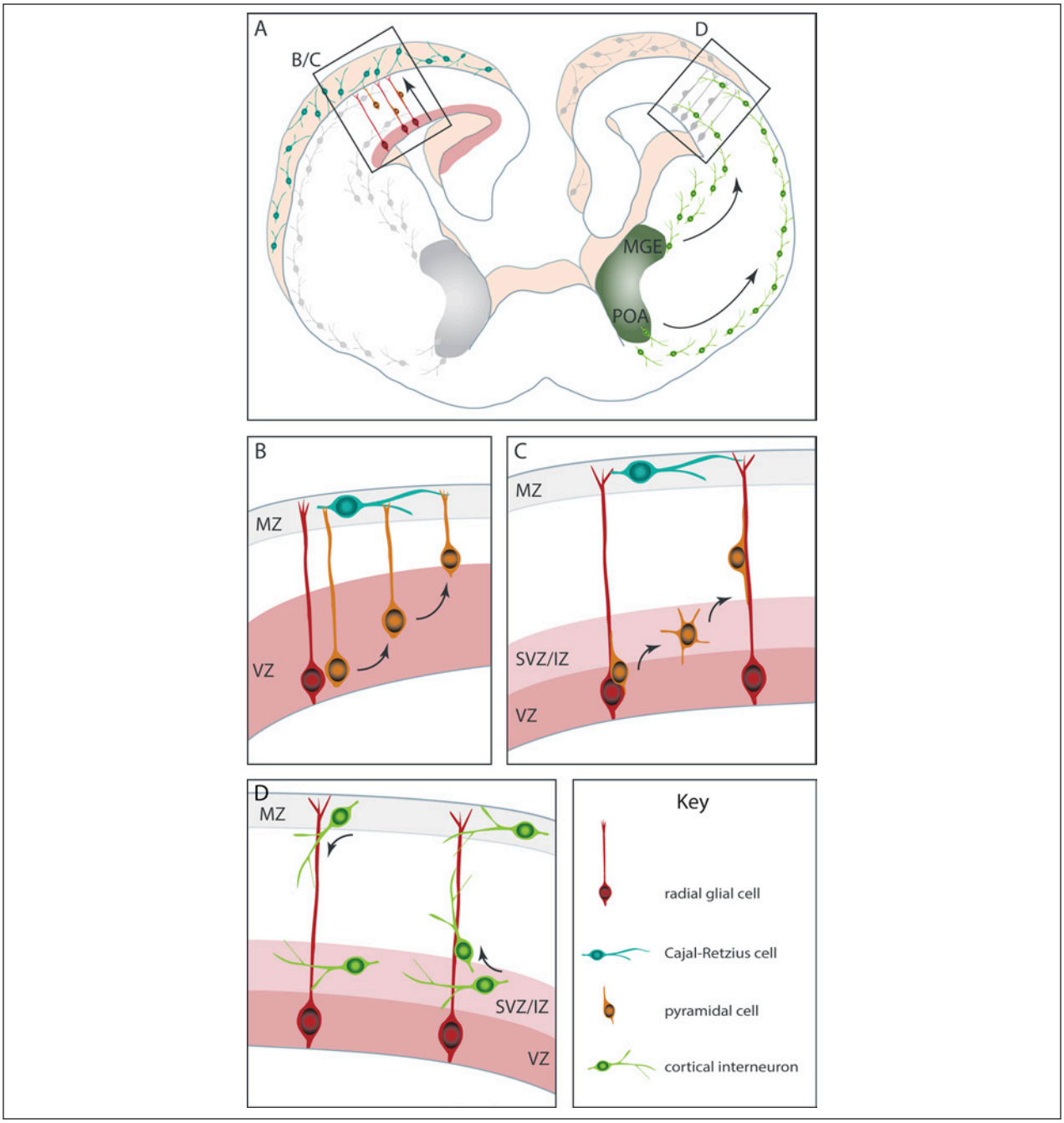

Figure 1. Different modes of neural migration in the embryonic forebrain. (A) Schematic coronal overview of radial and tangential migration during embryogenesis. Cajal–Retzius cells originating from the hem, ventral pallium, and septum migrate tangentially and distribute over the cortical surface. Radial glia progenitors generate pyramidal neurons that migrate radially toward the pia. Progenitors in the medial and caudal ganglionic eminence (MGE and CGE [caudal from the MGE, not shown], respectively) and the pre-optic area (POA) generate interneurons that migrate tangentially to the cortex. (B) First, neurons migrate by somal translocation. (C) Later-born neurons migrate along the glial scaffold. (D) Cortical interneurons disperse tangentially through the cortex via defined routes in the subventricular zone (SVZ)/intermediate zone (IZ) and the marginal zone (MZ). To invade the cortical plate interneurons switch to radial migration.

The Pivotal Role of N-Cad and Reelin

Cell–cell contact or short-timed adhesion often implicates the interaction of Cadherins or Cadherin-related molecules (Solecki 2012). A central molecule in adhesion of radially migrating neurons is N-Cadherin (N-Cad, Cdh2). N-Cad typically interacts in a homophilic way with another N-Cad

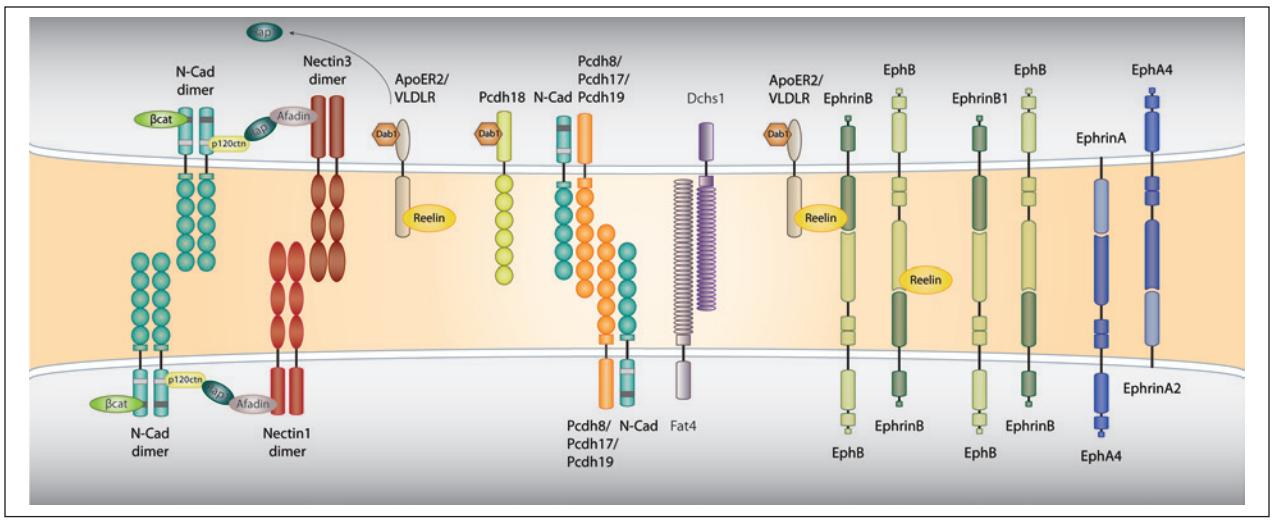

Figure 2. Molecular cross-talk at the membrane of migrating neurons. Overview of the variety of recently shown molecular interactions at the cell membrane between migrating neurons and other neurons they encounter on their path, as described in this update. Molecules such as N-Cad and Eph/Ephrins are engaged in different complexes, depending on the type of interaction and the migration mode.

molecule on the same cell (in *cis*) and an N-Cad duo on the adjacent cell (in *trans*) (Fig. 2).

During radial migration, young postmitotic neurons in the cortical intermediate zone polarize and concentrate N-Cad on their plasma membrane where the first neurite will form. Down-regulation of N-Cad by in utero electroporation of dominant-negative D390N-Cadherin results in randomization of N-Cad accumulation at the switch from the multipolar to bipolar phase and therefore in a delay of polarization and migration (Gärtner and others 2012). In tangential migration, N-Cad has a similar crucial role in polarization. Depletion of N-Cad in the MGE severely affects its organization and blocks the exit of neurons from the MGE. In vitro time-lapse experiments indicated that loss of N-Cad affects the motility and directionality of migrating interneurons by increasing the number of polarity switches (Luccardini and others 2013).

The presence of N-Cad on the cell membrane needs to be precisely regulated. One of the molecules that can accumulate N-Cad on the membrane is Rap1, a Ras-related GTPase that is activated downstream of Reelin signaling (Jossin and Cooper 2011). Reelin, secreted by Cajal–Retzius cells in the marginal zone of the cortex, is a well-known regulator of neuronal migration and positioning (Jossin and others 2003). Reelin binds to the ApolipoproteinE receptor 2 (ApoER2) and the very low density lipoprotein receptor (VLDLR) and induces phosphorylation of Disabled1 (Dab1), which in turn activates Rap1 (Fig. 2). Rap1 plays an important role during radial migration in the cortex. Without Rap1, cortical pyramidal neurons still polarize, but leading process stabilization and nuclear translocation is affected (Franco and others 2011). Nuclear translocation seems to be dependent on the coherent action of Cadherins and Nectins during glial-independent migration. Initial adhesion between Cajal–Retzius cells and migrating early-born neurons by Nectin1 and Nectin3, respectively, is stabilized by binding of Afadin and Rap1 to the Nectin intracellular domain (Fig. 2), in which Rap1 functions as a bridge between Afadin and p120ctn, connecting N-Cad to the Nectin complex. N-Cad simultaneously engages in homophilic interactions resulting in the consolidation of the adhesion point, which is crucial for nuclear translocation (Gil-Sanz and others 2013) (Fig. 2).

Contribution of Other Cadherins

Dab1 itself also links more directly to cell adhesion, as it was shown to interact with Protocadherin18, a member of the nonclustered delta-protocadherins (Homayouni and others 2001). The delta2-type Protocadherins (Pcdh) are not adhesive on their own, but homophilic interaction of Pcdh19, Pcdh17, or Pcdh8 in *trans* becomes adhesive on heterophilic interaction in *cis* with N-Cad (Fig. 2). Mutations in delta-protocadherins, as well as in different Cadherins, lead to severe encephalopathies and neurodevelopmental disorders such as intellectual disability, autism, schizophrenia, and early-onset epilepsy, underscoring their essential function during brain development (Redies and others 2012). Furthermore, the atypical giant Cadherins Fat4 and Dachsous1 (Dchs1), interacting as a receptor-ligand pair, are essential for neuronal migration in cortical development (Fig. 2). Mutations affecting

either of these molecules cause very similar syndromes in humans (Van Maldergem syndrome 1 and 2), characterized by heterotopia in the brain. Interestingly, knockdown of Fat4 or Dchs1 in the developing mouse cortex impairs neuronal migration (Cappello and others 2013). Other members of the nonclustered Protocadherins, named Celsr1–3, are involved in planar cell polarity and have important functions during brain development and neuron migration (Boutin and others 2012). Celsr3 has a role during the migration of cortical interneurons (Ying and others 2009); however, the ligands to these intriguing receptors still remain to be identified.

Eph/Ephrin Signaling Influences Different Migration Modes

Besides binding lipoprotein receptors, Reelin also signals through other receptors, such as Ephrin/Eph. Ephrin/Eph signaling operates in a bidirectional way. Ephrins are membrane-bound proteins that act as ligands for Eph receptors on the adjacent cell ("forward signaling"). Signaling can also occur through the Ephrin ligand intracellular domain ("reverse signaling"), enabling a cellular communication system crucial for migrating neurons (Klein and Kania 2014; Rodger and others 2012). Binding of Reelin to EphrinB induces clustering of ApoER2 and VLDLR and stabilization of Reelin signaling and Dab1 phosphorylation (Sentürk and others 2011) (Fig. 2). Moreover, Reelin can also bind to the EphB2 receptor independently of ApoER2 and VLDLR and activates EphB forward signaling in vitro (Bouché and others 2013) (Fig. 2). Taken together, the Ephrin/Eph pathway and Reelin signaling are interconnected in several ways.

Besides affecting radial migration, the tangential spread of cortical neurons and the formation of radial columns are regulated by EphrinB1. An excess of this molecule induces increased packing of pyramidal neurons in radial columns, whereas reduced EphrinB1 results in neuronal spreading. Overexpression of mutant EphrinB1 unable to interact with Eph-receptors does not result in increased clustering, suggesting that reverse signaling through EphrinB1 is essential for proper packing of neurons in columns (Dimidschstein and others 2013) (Fig. 2).

The efficient dispersion and distribution of Cajal–Retzius cells over the cortical surface is regulated by repulsive cell–cell contacts mediated by Eph/Ephrin interactions. Blocking of Eph/Ephrin signaling both in vitro and in vivo impairs contact repulsion in Cajal–Retzius cells and disrupts the efficient spreading of these neurons (Villar-Cerviño and others 2013) (Fig. 2). Interestingly, neurons do not limit themselves to the expression of either ligand or receptor. Migrating interneurons, for example, express both EphrinA2 and EphA4. Forward signaling through EphA4 receptors on migrating interneurons prevents them from entering the ventricular zone of the MGE (Zimmer and others 2008) (Fig. 2). Furthermore, interneurons also interact with each other, while migrating and reverse signaling through EphrinA2 promotes cell motility (Steinecke and others 2014) (Fig. 2).

Future Perspectives

Taken together, these recent findings indicate that upon cell–cell contact, information is exchanged and processed in the migrating neurons. Similar molecular interactions might influence migration in other forebrain regions, such as the rostral migratory stream of olfactory bulb neurons generated after birth. Furthermore, several of the molecules involved in the cross-talk at the membrane lead to neurodevelopmental disorders when mutated in human, underlining their importance for brain development.

Interestingly, many of the known transmembrane components interact and cross-talk, and eventually all seem to be connected to each other through direct interaction or shared use of a common interacting factor. The presence of different combinations of common (for instance, N-Cad) but also similar and perhaps redundant (for instance, different Cadherins and Protocadherins) molecules enables the migrating neuron to recognize cells it encounters and also provides robustness to the system. Moreover, migrating neurons should be equipped with transmembrane molecules according to their specific needs, based on their identity and the position they will occupy in the adult brain. Pyramidal neurons destined to build cortical columns will therefore express a different set of membrane-bound molecules compared to tangentially migrating interneurons or Cajal–Retzius cells. Nevertheless, disruption of the laminar distribution of pyramidal neurons, for instance, affects the positioning of cortical interneurons, demonstrating that neuronal cell types of different classes influence each other's final allocation (reviewed in Bartolini and others 2013). This shows that, even if neuronal identity is intrinsically defined, its migration route and final allocation critically depend on the non-cell-autonomous information gathered from interactions with other neurons. We believe that further understanding of brain development and the cause of neurodevelopmental disorders will benefit from the elucidation of the molecular nature of this cross-talk.

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